Efficacy and safety of dupilumab in patients with severe chronic rhinosinusitis with nasal polyps (LIBERTY NP SINUS-24 and LIBERTY NP SINUS-52): results from two multicentre, randomised, double-blind, placebo-controlled, parallel-group phase 3 trials

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Summary

Background

Patients with chronic rhinosinusitis with nasal polyps (CRSwNP) generally have a high symptom burden and poor health-related quality of life, often requiring recurring systemic corticosteroid use and repeated sinus surgery. Dupilumab is a fully human monoclonal antibody that inhibits signalling of interleukin (IL)-4 and IL-13, key drivers of type 2 inflammation, and has been approved for use in atopic dermatitis and asthma. In these two studies, we aimed to assess efficacy and safety of dupilumab in patients with CRSwNP despite previous treatment with systemic corticosteroids, surgery, or both.

Methods

LIBERTY NP SINUS-24 and LIBERTY NP SINUS-52 were two multinational, multicentre, randomised, double-blind, placebo-controlled, parallel-group studies assessing dupilumab added to standard of care in adults with severe CRSwNP. SINUS-24 was done in 67 centres in 13 countries, and SINUS-52 was done in 117 centres in 14 countries. Eligible patients were 18 years or older with bilateral CRSwNP and symptoms despite intranasal corticosteroid use, receiving systemic corticosteroids in the preceding 2 years, or having had sinonasal surgery. Patients in SINUS-24 were randomly assigned (1:1) to subcutaneous dupilumab 300 mg or placebo every 2 weeks for 24 weeks. Patients in SINUS-52 were randomly assigned (1:1:1) to dupilumab 300 mg every 2 weeks for 52 weeks, dupilumab every 2 weeks for 24 weeks and then every 4 weeks for the remaining 28 weeks, or placebo every 2 weeks for 52 weeks. All patients were randomly assigned centrally with a permuted block randomisation schedule. Randomisation was stratified by asthma or non-steroidal anti-inflammatory drug-exacerbated respiratory disease status at screening, previous surgery at screening, and country. Patients with or without comorbid asthma were included. Coprimary endpoints were changes from baseline to week 24

in nasal polyp score (NPS), nasal congestion or obstruction, and sinus Lund-Mackay CT scores (a coprimary endpoint in Japan), done in an intention-to-treat population. Safety was assessed in a pooled population of both dupilumab groups in SINUS-52 up to week 24 and the dupilumab group in SINUS-24 and the placebo groups in both studies until week 24. The trials are complete and registered at ClinicalTrials.gov, NCT02912468 and NCT02898454.

Findings

Between Dec 5, 2016, and Aug 3, 2017, 276 patients were enrolled in SINUS-24, with 143 in the dupilumab group and 133 in the placebo group receiving at least one study drug dose. Between Nov 28, 2016, and Aug 28, 2017, 448 patients were enrolled in SINUS-52, with 150 receiving at least one dose of dupilumab every 2 weeks, 145 receiving at least one dose of dupilumab every 2 weeks for 24 weeks and every 4 weeks until week 52, and 153 receiving at least one dose of placebo. Dupilumab significantly improved the coprimary endpoints in both studies. At 24 weeks, least squares mean difference in NPS of dupilumab treatment versus placebo was −2·06 (95% CI −2·43 to −1·69; p<0·0001) in SINUS-24 and −1·80 (−2·10 to −1·51; p<0·0001) in SINUS-52; difference in nasal congestion or obstruction score was −0·89 (−1·07 to −0·71; p<0·0001) in SINUS-24 and −0·87 (−1·03 to −0·71; p<0·0001) in SINUS-52; and difference in Lund-Mackay CT scores was −7·44 (−8·35 to −6·53; p<0·0001) in SINUS-24 and −5·13 (−5·80 to −4·46; p<0·0001) in SINUS-52. The most common adverse events (nasopharyngitis, worsening of nasal polyps and asthma, headache, epistaxis, and injection-site erythema) were more frequent with placebo.

Interpretation

In adult patients with severe CRSwNP, dupilumab reduced polyp size, sinus opacification, and severity of symptoms and was well tolerated. These results support the benefits of adding dupilumab to daily standard of care for patients with severe CRSwNP who otherwise have few therapeutic options.

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